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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/821,139	03/29/2001	Laura S. Lehman	7960-131	5628

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EXAMINER
HAGHIGHATIAN, MINA

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 11/05/2002 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/821,139	LEHMAN ET AL.	
	Examiner	Art Unit	
	Mina Haghighatian	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 21-29, 36-38 and 47-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marketing Authorization for Pramidin (hereinafter Pramidin) in view of Robins (product information on Reglan®).

Pramidin discloses Pramidin 10 and Pramidin 20 compositions, where each ml solution contains metoclopramide hydrochloride monohydrate, corresponding to 200 or 400 mg metoclopramide free base respectively. Pramidin also contains purified water and other ingredients such as sorbitol and sodium acetate.

Pramidin is supplied in nasal spray form, and is indicated for therapeutic uses such as in nausea and vomiting induced by antineoplastics and other medications, digestive disorders and symptomatologic treatment of gastro-esophageal reflux, of duodenal-gastric billiary reflux and gastroparesis of various origin such as diabetic neuropathy, etc.

Dosage of Pramidin recommended for treatment of functional dyspepsia or other disorders of gastrointestinal motility is 1 puff of 10 mg in the same nostril 2-3 times daily (20-30mg). The drug must be administered before meals. For treatment of nausea/vomiting dosage is recommended at 20 mg in each nostril 3 times a day (120mg). In cases of delayed nausea/vomiting the dosage is 120-160mg/day.The

instruction for use are also described. Pramidin lacks specific teachings on the duration of treatment.

Robins discloses metoclopramide monohydrochloride monohydrate in tablet, syrup and solution for injection. Metoclopramide is said to stimulate motility of the upper gastrointestinal tract without stimulating gastric, biliary or pancreatic secretions (see bottom of page 2). Robins also discloses that Reglan® (metoclopramide hydrochloride) is indicated for the relief of symptoms associated with acute and recurrent diabetic gastric stasis. The usual manifestations of delayed gastric emptying (e.g, nausea, vomiting, heartburn, persistent fullness after meals and anorexia) appear to respond to Reglan® within different time intervals (see Indications and Usage on page 5).

Robins also discloses the appropriate dosages for the use of metoclopramide. For the relief of symptoms associated with diabetic gastroparesis, 10mg of metoclopramide 30 minutes before each meal and at bedtime for **two to eight weeks**. Lower doses (2.5- 5 mg) or 0.1 mg/kg are recommended for pediatric patients and elderly, thus meeting limitations of claims 2-4, 6-8, 10-12 and 18-20 (see page 12).

Robins also discloses that metoclopramide solutions can be mixed with other active agents(drugs) such as cimetidine, mannitol, ascorbic acid, clindamycin, insulin etc (see page 13).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have combined the teachings of Pramidine on intranasal administration of metoclopramide for treating gastroparesis with the duration of therapy

as taught by Robins because of the need for treating a specific disorder with the appropriate therapy and its duration.

Claims 30-35, 39-46 and 49-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marketing Authorization for Pramidin (hereinafter Pramidin).

Pramidine is discussed above.

Although the Pramidin document does not specifically disclose a daily dosage for treating gastroparesis, the disclosed daily dosage recommendations are within the required range and it would have been obvious to a person of ordinary skill in the art at the time the invention was made to have implemented slight modifications to the teachings in order to have obtained a method of treatment for a specific disorder with a known product at suggested dosage ranges. Also noted that optimization of concentration ranges will not support the patentability of subject matter.

Claims 21-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robins (product information on Reglan®) in view of Wenig (4,624,965).

Robins discloses metoclopramide monohydrochloride monohydrate in tablet, syrup and solution for injection. Metoclopramide is said to stimulate motility of the upper gastrointestinal tract without stimulating gastric, biliary or pancreatic secretions (see bottom of page 2). Robins also discloses that Reglan® (metoclopramide hydrochloride) is indicated for the relief of symptoms associated with acute and recurrent diabetic gastric stasis. The usual manifestations of delayed gastric emptying (e.g, nausea,

vomiting, heartburn, persistent fullness after meals and anorexia) appear to respond to Reglan® within different time intervals (see Indications and Usage on page 5).

Robins also discloses the appropriate dosages for the use of metoclopramide. For the relief of symptoms associated with diabetic gastroparesis, 10mg of metoclopramide 30 minutes before each meal and at bedtime for two to eight weeks. Lower doses (2.5- 5 mg) or 0.1 mg/kg are recommended for pediatric patients and elderly (see page 12).

Robins also discloses that metoclopramide solutions can be mixed with other active agents(drugs) such as cimetidine, mannitol, ascorbic acid, clindamycin, insulin etc (see page 13). Robins lacks teachings on nasal preparations of metoclopramide.

Wenig teaches nasal administration of known anti-nausea and anti-emetic therapeutic agents and dosage forms useful for such administration. Metoclopramide is one of the preferred compounds for use in the nasal preparation because when low dosages are administered nasally high blood levels are rapidly achieved and maintained for a long period of time. Preferred nasal dosage forms are solutions, suspensions and gels, which normally contain a major amount of water (preferably purified water) in addition to the active agent. If desired, sustained release nasal compositions, e.g, sustained release gels, or when a more highly insoluble form is desired, a long chain carboxylic acid salt of the desired drugs can be conveniently employed (col. 5, lines 8-12; 44-60).

Wenig discloses compositions for nasal drops or nasal spray. Composition C is shown to contain metoclopramide, water and additives which bring the final concentration to 10 mg/ 0.2 ml (see Example 1 in column 6).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the Reglan® preparations of Robins by using the nasal administration of metoclopramide taught by Wenig with the reasonable expectations of preparing a nasal preparation of metoclopramide for treating gastroparesis, which is pain free, economical and more efficient than oral administration.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure, Tyers (5,578,632).

Tyers discloses the use of anti-emetic agents such as metoclopramide for stimulation of gastric motility. Tyres also discloses a method of treatment for the relief of nausea and vomiting, and/or the promotion of gastric emptying e.g. for the relief of gastrointestinal disorders associated with gastric stasis.

Response to Arguments

Applicant's arguments filed 08/14/02 have been fully considered but they are not persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by **combining or modifying** the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it is clearly shown that Pramidin discloses a nasal spray formulation comprising metoclopramide in a daily dosage of about 40 mg or higher for treatment of disorders of gastric system. Robins teaches that in the same daily dosage range, the treatment is for 2 to 8 weeks. It would have been obvious to a person of ordinary skill in the art to make use of the already disclosed optimum duration of time for the therapy, without any need for experimentation, in modifying the preparation of Pramidin.

Applicant argues that "Pramidin does not teach administering metoclopramide intranasally for periods as long as about 2 weeks to about 8 weeks". Applicant is correct, however, the original claims 1-12 and 15-17, and the new claims 30-35, 39-46 and 49-51, which are rejected over Pramidin reference, do not contain the limitation of a duration of therapy. Pramidin clearly meets all the limitations of the said claims.

Applicant argues that the Wenig reference is silent as to the merits of metoclopramide for the specific treatment of gastroparesis. Although this is a correct statement, it is noted that the intranasal formulations of metoclopramide are taught to be used for treating gastric disorders such as emesis and nausea. However, the importance of the Wenig reference to one of ordinary skill in the art is that it teaches metoclopramide as a nasal formulation. The skilled artisan can then transfer this teaching into method of treatment as taught by Robins.

Applicant also argues that Wenig teaches no protocol for administering either nasal spray or drop formulation for treatment of symptoms in humans. This is not persuasive because Wenig repeatedly refers to "administered to mammals" in both the reference and in claims (and mammals clearly encompasses humans), as well as referring to human patients in examples 8 and 9. Also noted that studies are generally performed on animals.

Applicant argues that Wenig teaches dosages of 5mg, 10mg and 20mg in example 8 and do not teach one skilled in art the applicable therapeutically effective dosages for a nasal spray formulation. This is not persuasive because example 8, in lines 51 to 53 reads "the study was extended to dosage levels of 20mg and 40mg by the intranasal route using the same composition". A dose of 20mg or 40mg, 2 to 4 times a day is well within the proposed daily dosage range in the instant claims.

Applicant is reminded that **combining or modifying** the teachings of the prior art to produce the claimed invention establishes obviousness.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is 703-308-6330. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jose Dees can be reached on 703-308-4628. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.

Mina Haghighatian
November 1, 2002

MICHAEL G. HARTLEY
PRIMARY EXAMINER